Endometrial Carcinoma Risks among Menopausal Estrogen plus Progestin and Unopposed Estrogen Users in a Cohort of Postmenopausal Women

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Abstract

Background: **Because unopposed estrogen substantially increases endometrial carcinoma risk, estrogen plus progestin is one menopausal hormone therapy formulation for women who have not had a hysterectomy. However, endometrial carcinoma risks among estrogen plus progestin users and among former unopposed estrogen users are not firmly established.**

Methods: **We evaluated endometrial carcinoma risks associated with estrogen plus progestin and unopposed estrogen therapies in 30,379 postmenopausal Breast Cancer Detection Demonstration Project follow-up study participants. We ascertained hormone therapy use and other risk factors during telephone interviews and mailed questionnaires between 1979 and 1998. We identified 541 endometrial carcinomas via self-report, medical records, the National Death Index, and state cancer registries. Poisson regression generated time-dependent rate ratios (RR) and 95% confidence intervals (95% CI).**

Results: **Endometrial carcinoma was significantly associated with estrogen plus progestin only use (n = 68 cancers; RR, 2.6; 95% CI, 1.9-3.5), including both sequential (progestin <15 days per cycle; n = 32 cancers; RR, 3.0; 95% CI, 2.0-4.6) and continuous (progestin at least 15 days per cycle; n = 15 cancers; RR, 2.3; 95% CI, 1.3-4.0) regimens. The RR increased by 0.38 (95% CI, 0.20-0.64) per year of estrogen plus progestin use, and RRs increased with increasing duration of use for both regimens. The strong association with unopposed estrogen use declined after cessation but remained significantly elevated ≥10 years after last use (RR, 1.5; 95% CI, 1.0-2.1).**

Conclusions: **Both estrogen plus progestin regimens significantly increased endometrial carcinoma risk in this study. Risks among unopposed estrogen users remained elevated long after last use. The prospect that all estrogen plus progestin regimens increase endometrial carcinoma risk deserves continued research.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1724–31)

Introduction

The strong association between endometrial carcinoma and use of unopposed estrogen (1) led to curtailed use of this formulation since the 1980s by postmenopausal women without hysterectomy. Unopposed estrogen therapy remained an option for women after hysterectomy (2) and various combined estrogen plus progestin regimens became preferable for women without hysterectomy (3).

Twenty years after estrogen plus progestin use began to increase (4), questions remain about its association with endometrial cancer. Epidemiologic studies generally agree that sequential estrogen plus progestin regimens (i.e., daily estrogen plus progestin added for <15 days per cycle) significantly increase endometrial cancer risk although not as much as unopposed estrogen does (5-9). The conclusion that continuous estrogen plus progestin regimens (i.e., daily estrogen plus progestin added for at least 19 days and up to every day per cycle) do not increase risk (10-12) is based on relatively few studies, limited by inadequate statistical power due to small numbers of exposed cases, and complicated by inconsistently defined continuous estrogen plus progestin exposures. Early observational data reported null (5) and inverse (6) associations with continuous regimens, but two recent epidemiologic studies published increased risks similar to those observed in sequential regimen users (7, 8). Most recently, a study of 716,738 postmenopausal United Kingdom women without hysterectomy reported null associations with sequential estrogen plus progestin use (both short-term and long-term use) and long-term (≥5 years) continuous estrogen plus progestin use but significantly inverse associations with short-term (<5 years) continuous regimen use (13).

Some women without hysterectomy continue to use unopposed estrogen in the United States (14). The increased risks decline after cessation of use (1), but whether or when they return to the level of women who never used menopausal hormones is not known. Imprecision (15, 16), inconsistency (8), and incomplete assessment of both duration and recency (7) limit the current estimates of 2-fold elevated risks ≥10 years after last use.

To address these unanswered questions about estrogen plus progestin therapy and unopposed estrogen therapy, we analyzed data from the National Cancer Institute Breast Cancer Detection Demonstration Project (BCDDP) follow-up study.

Materials and Methods

Study Population. In 1979, the National Cancer Institute established the BCDDP follow-up study of 61,430 (96%) of 64,182 volunteers (4,275 women diagnosed with breast cancer; 25,114 women who underwent breast surgery for benign disease; 9,628 women recommended for surgical consultation, which was not done; and 25,165 women sampled from women who had neither surgery nor recommendation for surgical consultation during screening) selected from the original 283,222 participants in the initial

Received 2/10/05; revised 4/14/05; accepted 4/19/05.

Grant support: National Cancer Institute intramural funds.

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Note: Presented at the 2003 Annual Meeting of the American College of Epidemiology, Chicago, Illinois.

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screening phase. Follow-up consisted of four phases. Phase 1 (1979-1986) used a baseline telephone interview and up to six (usually four) annual telephone follow-up interviews through 1986. Phases 2 to 4 used single, self-administered, mailed questionnaires (1987-1989, 1993-1995, and 1995-1998, respectively). Respondents who were not known to be deceased received each subsequent mailed questionnaire. We interviewed nonrespondents by telephone, when possible. The National Cancer Institute Institutional Review Board approved the study. All participants provided informed consent. Previous publications described the study in more detail (17).

Exposure Assessment. Each data collection phase used slightly different methods to ascertain hormone therapy formulation (i.e., unopposed estrogen versus estrogen plus progestin) and regimen (i.e., number of days progestin per cycle). Phase 1 interviews collected information on age at first use of hormone therapy but did not distinguish the two formulations. The phase 2 to 4 questionnaires queried unopposed estrogen and estrogen plus progestin (i.e., estrogen and progestin pills taken in the same month) use, including duration of use, and the phase 3 and 4 questionnaires collected pill names and doses. Only the phase 4 questionnaire (1995-1998) specifically asked about estrogen and progestin taken in the same pill.

The phase 2 and 3 questionnaires asked about the number of days progestin pills were taken each cycle. The latter also asked women who did not know their regimen whether progestin usage was for at least 15 days per cycle. The phase 4 questionnaire used only categories (<10, 10-14, 15-19, or 20-25 days per month or every day for progestin pill users; or Prempro versus Premphase for combination pill users) to differentiate regimens.

Each phase included questions about current menopausal status, gynecologic surgeries (e.g., type and dates of surgery), and other risk factors. Interviews during the screening phase (1973-1980) collected demographic data (e.g., education level and ethnicity) and measured height and weight (18).

Analytic Data Set. We excluded the following women from the original cohort of 61,430 women: women with hysterectomy (n = 24,376), death (n = 23), or endometrial (n = 16) or breast cancer before the start of follow-up (n = 2,825); women who reported no menarche (n = 9), natural menopause before age 35 years (n = 130), or menopause due to bilateral oophorectomy (n = 1,555) or radiation (n = 545); premenopausal women (n = 66); women with missing data on menopausal status (n = 1,380) or date (n = 112); and women who developed nonepithelial uterine cancers (n = 14). Analysis included 30,379 postmenopausal women who had a natural menopause before baseline or during follow-up.

Cancer Ascertainment. We identified women with endometrial carcinoma based on self-report and linkage to state cancer registries and the National Death Index. For self-reported cancers, we sought medical records that were abstracted using standardized forms. To maximize end point ascertainment (19), we linked 72% of the women who completed a baseline interview and 85% of the women who completed a phase 2 questionnaire to state cancer registries. We retrieved cause of death information (including date of diagnosis, when available) from death certificates.

The final carcinoma group included 541 women identified from medical records (n = 360), registry data (n = 105), death certificates (n = 39), and self-report only (n = 37). Women whose self-reported endometrial cancers were refuted by medical record review (n = 49) or lacked a diagnosis or hysterectomy date (n = 9) were censored as non-events. Overall, 79.4% of self-reported carcinomas were confirmed by records, registries, or death certificates. We defined diagnosis date hierarchically from medical records, state cancer registry data, self-report, or, when no other date of diagnosis was available, date of death from death certificates.

Analysis. Follow-up began at the baseline interview date or menopause date, whichever was later. We defined menopause as no menstrual period for at least 3 months. Person-years accrued until the earliest of the following dates: endometrial carcinoma diagnosis, hysterectomy, death, or phase 4 questionnaire completion. Based on the National Death Index and cancer registry linkages, we assumed women without a phase 4 questionnaire were alive and disease-free (19). These women contributed person-time until the date of last contact (e.g., a notice of refusal to participate) or the date that we estimated they would have completed the phase 4 questionnaire, which we assigned based on the average time interval between completed questionnaires (18).

All 30,379 women completed a phase 1 interview; 26,235 (86.4%), 23,090 (76.0%), and 22,048 (72.6%) completed phase 2 to 4 questionnaires, respectively. Death (2.2%), refusal (3.4%), illness (0.9%), or inability to contact before the end of that phase (i.e., lost to follow-up; 7.1%) accounted for missing phase 2 questionnaires. Those proportions for phase 3 and 4 questionnaires were 8.3%, 2.6%, 1.0%, and 12.1%, respectively, and 12.6%, 4.2%, 1.7%, and 8.9%, respectively.

We computed time-dependent hormone therapy variables up to 1 year before attained (i.e., current) age. Women who used more than one formulation or regimen during follow-up contributed person-time to multiple categories. When exposure status or duration became unknown, subsequent person-years went to the ''unknown'' category (17).

Estrogen plus progestin exposure included both pills taken together and combination estrogen plus progestin pills. We based estrogen plus progestin regimen variables on the reported number of days progestin pills were taken each month. For consistency across questionnaires, we categorized regimen as sequential (progestin used for <15 days per month), continuous (progestin used for ≥15 days per month), or unknown. Because progestin use was not collected until the phase 2 questionnaire, exposed person-time and cancers from estrogen therapy users who only completed the phase 1 interviews were included in the ''estrogen, unknown progestins'' category.

We used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI) using standard likelihood ratio methods (20). For continuous exposures, such as duration of menopausal hormone use, we fit the linear excess RR model $\lambda\ (t, z, d) = \lambda\ (t, z, 0)\ (1 + \beta d)$, where d is duration of hormone use, the variable β is the change in the excess RR (RR − 1) per unit d, $\lambda\ (t, z, 0)$ is the risk at time t for women with covariate vector z and no hormone use, and $\lambda\ (t, z, d)$ is the risk at time t for women with covariate vector z and d years of hormone use. [The linear excess RR model fit the data better than a log-linear excess RR model (likelihood ratio test P = 0.36).] We used likelihood-based methods to obtain 95% CIs for the linear excess RR model (21). We assessed statistical significance of trends using a score test. Never-use of menopausal hormones was the reference group for all RRs.

For the Poisson regression, we summarized person-time in a multidimensional table defined by categories of attained age (seven categories: <55, 55-59, 60-64, 65-59, 70-74, 75-79, and ≥80 years) and calendar time (four categories: 1979-1983, 1984-1988, 1989-1993, and 1994-1998) as well as hormone therapy variables, household income, age at menarche, parity, duration of oral contraceptive use, smoking, and body mass index [BMI (kg/m^2); based on measurements from the last screening visit before the baseline interview]; see Table 2 for categories of the last

six variables. Final models included adjustment for these confounders. Hormone therapy, attained age, calendar time, and smoking variables were all time-dependent.

Results

The mean age at the start of follow-up was 57.2 years. The average duration of follow-up was 13.0 years (range, 1 month-19.8 years). The cohort accrued 397,175 person-years of follow-up. The median year of carcinoma diagnosis was 1990 (25th percentile, 1986; 75th percentile, 1994).

Risk Factors. Risk factors displayed the expected associations with endometrial carcinoma (Table 1). Older age, white race/ethnicity, and lower BMI were associated with hormone therapy use. Higher levels of education and income were associated with estrogen plus progestin. Ages at menarche and menopause, oral contraceptive use, parity, and smoking were all associated with both formulations but in opposite directions. Younger age, less education, lower income, and higher BMI were associated with unknown hormone therapy use.

Estrogen plus Progestin Therapy. The overall RR for any estrogen plus progestin use was 2.7 (95% CI, 2.1-3.5). This was similar to the RRs for estrogen plus progestin after unopposed estrogen use (RR, 2.8; 95% CI, 2.0-3.8) and estrogen plus progestin only use (RR, 2.6; 95% CI, 1.9-3.5). The person-time weighed mean durations of estrogen and estrogen plus progestin use were 4.0 and 3.4 years, respectively, in women who used both formulations. The person-time weighed mean

Table 1. Distribution of person-years according to hormone therapy formulation and selected endometrial carcinoma risk factors

	No hormone therapy (%)	Unopposed estrogens (%)	Estrogen plus progestin (%)	Estrogen, unknown progestin (%)	Total person-years*	RR (95% CI)
Attained age (y)						
<55	73	12	5	3	7,449	1.0 (Reference)
55-59	65	12	12	4	42,402	1.2 (0.4-3.3)
60-64	55	15	19	5	85,392	1.6 (0.6-4.3)
65-69	50	19	19	7	90,522	2.7 (0.98-7.3)
70-74	48	22	16	9	73,081	3.2 (1.2-8.7)
75-79	48	24	12	11	48,633	3.3 (1.2-9.2)
≥80	53	22	7	12	49,696	3.0 (1.1-8.0)
Race/ethnicity						
White	50	21	17	6	295,598	1.0 (Reference)
Non-White	60	13	9	13	101,577	0.8 (0.7-0.99)
Formal education						
Less than high school	58	18	7	10	50,492	1.0 (Reference)
High school graduate	55	19	13	7	162,565	1.2 (0.9-1.5)
Beyond high school	49	18	20	7	184,118	1.3 (0.99-1.7)
Household income in 1973						
<$10,000	59	18	7	9	80,324	1.0 (Reference)
$10,000-29,999	52	19	16	7	247,940	1.4 (1.1-1.8)
≥$30,000	45	19	24	7	50,772	1.8 (1.3-2.4)
Unknown	56	19	10	8	18,139	0.6 (0.4-1.2)
Age at menarche (y)						
≤11	53	17	16	7	61,083	1.0 (Reference)
12-13	52	19	16	7	220,860	1.0 (0.8-1.3)
≥14	54	19	13	8	115,232	0.7 (0.6-0.97)
Age at menopause (y)						
≤48	52	22	12	9	94,630	1.0 (Reference)
49-51	54	18	15	7	169,026	0.9 (0.7-1.1)
≥52	52	17	18	7	133,518	1.1 (0.8-1.3)
Oral contraceptive use (y)						
None	56	20	12	7	293,567	1.0 (Reference)
≤2	44	16	25	7	46,036	1.1 (0.9-1.5)
>2	44	13	26	8	56,601	0.7 (0.5-0.9)
Unknown	30	16	15	19	971	0.7 (0.1-5.2)
Parity						
0	53	21	13	8	60,247	1.0 (Reference)
1 or 2	52	20	15	8	164,313	0.9 (0.7-1.1)
≥3	54	17	16	7	172,615	0.6 (0.5-0.8)
BMI (kg/m^2)						
<18.5	47	18	19	10	8,847	0.8 (0.4-1.6)
18.5-24.9	49	19	18	8	253,801	1.0 (Reference)
25-29.9	58	18	11	8	91,757	1.0 (0.8-1.2)
30-34.9	63	15	7	7	24,355	1.5 (1.1-2.1)
≥35	68	14	6	5	8,866	2.5 (0.7-3.7)
Unknown	59	14	14	6	9,549	0.8 (0.4-1.5)
Smoking status						
Never	53	20	16	5	207,498	1.0 (Reference)
Current	53	24	11	6	49,335	0.7 (0.5-0.97)
Former	46	19	22	6	99,116	1.1 (0.9-1.3)
Unknown	68	3	1	25	41,226	1.1 (0.8-1.4)
BCDDP participant type						
Surgery for benign breast disease	53	19	15	8	158,133	1.0 (Reference)
No breast disease or surgery	52	18	15	8	172,714	1.0 (0.8-1.2)
Recommended for surgery	54	18	15	7	66,328	1.0 (0.8-1.3)

NOTE: RRs adjusted for attained age and calendar time.

*Percentages do not sum to 100 because some hormone therapy formulations are not included: progestins only or progestins with unknown estrogen use (3,404 person-years) and unknown hormone therapy use (21,256 person-years).

duration of estrogen plus progestin use was 3.6 years in women who used only estrogen plus progestin. To avoid the potential influence of prior unopposed estrogen use, we restricted all subsequent analyses of regimen and duration to women who used only estrogen plus progestin. Hereinafter, ''estrogen plus progestin'' refers to use of only estrogen plus progestin in our data.

The RRs for both sequential and continuous regimens were significantly elevated (Table 2). Longer average durations of use among sequential users (3.9 years) than continuous users (3.0 years) may have contributed to the higher RR for sequential use. The RRs for both regimens increased with increasing duration ($P < 0.001$ for both), and the excess RRs per year of use were similar (0.45 and 0.52). These duration associations did not statistically differ between regimens ($P = 0.38$ for likelihood ratio test of homogeneity of duration of use for sequential versus continuous).

Because most of the carcinomas among estrogen plus progestin users occurred in current users, we limited analyses of risk after cessation to current versus former. Those RRs were comparable for both regimens (Table 2).

Increased RRs with any estrogen plus progestin use appeared across categories of smoking, parity, oral contraceptive use, and BMI. Few overweight or obese women with endometrial carcinoma had used estrogen plus progestin (data not shown).

Unopposed Estrogen Therapy. The adjusted RR for ever-use of unopposed estrogens only use was 2.7 (95% CI, 2.2-3.4). Among women who only used unopposed estrogens, the linear association with duration produced significantly elevated RRs for all categories, including short-term use (Table 3). Each additional year of use increased the RR by 0.58 (95% CI, 0.42-0.79).

Former use generated substantially lower RRs than current use. The RRs decreased with increasing time since last use, but the RR for last use at least 10 years ago remained significantly elevated.

The strength of the association with duration of unopposed estrogen use decreased as time since last use increased (Table 4). Increasing duration of use was significantly associated with endometrial carcinoma within each category of recency of use. The excess RR per year of use was lower among women who last used unopposed estrogens ≥10 years ago (0.19; 95% CI, 0.04-0.41) than among current or more recent users.

There was a statistical interaction ($P = 0.006$) between long-term unopposed estrogen use (i.e., ≥5 years) and BMI. The excess RR per year of use was 0.92 (95% CI, 0.61-1.35) among women with a normal weight (BMI, <25 kg/m^2), whereas the excess RRs per year of use among overweight women (BMI, 25-29 kg/m^2) and obese women (BMI, ≥30 kg/m^2) were 0.31 (95% CI, 0.12-0.62) and 0.05 (95% CI, undefined to 0.34), respectively. The excess RRs per year of use were similar across strata defined by smoking, parity, and oral contraceptive use. None of those interactions was statistically significant.

Other Analyses. The results did not change after excluding women who reported any use of other hormone therapy preparations (e.g., shots, patches, creams, or ''other''; 46,429 person-years and 76 endometrial carcinomas) or 37 women (336 person-years) whose carcinomas were not confirmed by medical records (data not shown).

Discussion

We observed statistically significant positive associations between estrogen plus progestin use and endometrial carcinoma. Both sequential and continuous estrogen plus progestin regimens generated similar associations with increasing duration of use, although the estimates were somewhat imprecise. These data contradict the hypothesis that use of estrogen plus progestin therapy that includes at least 12 to 15 days of progestin per cycle does not increase endometrial cancer risk (10-12).

Early epidemiologic studies that included low exposure frequencies (22) or preceded widespread combination therapy use in the United States (23-25) reported null associations between endometrial cancer and combination therapy use. Most subsequent studies found increased risks among women taking sequential estrogen plus progestin (5-8, 26). The data on continuous regimens are less consistent, but recent case-control studies found increased risks among continuous regimen users. One (7) reported a significantly increased odds ratio (OR) for >21 days of progestin per cycle (OR, 2.26; 95% CI, 1.27-4.00) based on 20 exposed cases and

Table 2. Estrogen plus progestin use and endometrial cancer

	No hormone therapy		Only estrogen plus progestin*		Only sequential estrogen plus progestin		Only continuous estrogen plus progestin	
	No./ person-years	RR (95% CI)	No./ person-years	RR (95% CI)	No./ person-years	RR (95% CI)	No./ person-years	RR (95% CI)
No Use	168/209,196	1.0 (Reference)†						
Any use			68/35,394	2.6 (1.9-3.5)	32/15,565	3.0 (2.0-4.6)	15/8,198	2.3 (1.3-4.0)
Duration of use (y)								
<2			23/16,779	2.1 (1.3-3.3)	5/5,890	1.3 (0.5-3.2)	3/3,840	1.1 (0.3-3.4)
2-3			13/7,224	2.7 (1.5-4.9)	7/3,907	2.4 (1.1-5.3)	6/2,133	3.9 (1.7-9.2)
4-5			9/5,186	2.4 (1.2-4.8)	5/2,658	2.5 (0.99-6.2)	3/1,307	2.9 (0.9-9.4)
≥6			23/6,205	4.4 (2.7-7.1)	15/3,110	5.7 (3.2-10.2)	3/918	4.2 (1.3-13.6)
P				<0.001		<0.001		<0.001
Excess RR per year				0.38 (0.20-0.64)		0.45 (0.22-0.80)		0.52 (0.15-1.13)
Recency of use‡								
Current use			31/16,914	2.6 (1.7-3.9)	18/8271	3.1 (1.8-5.3)	8/4,868	2.3 (1.1-4.9)
<5 y ago			8/6,739	1.6 (0.8-3.4)				
5-9 y ago			5/2,494	2.5 (0.99-6.1)	10/6132	2.1 (1.1-4.2)	5/2,622	2.4 (0.97-6.1)
≥10 y ago			5/2,012	3.1 (1.3-7.8)				

*Does not include 55 carcinomas and 24,503 person-years (RR, 2.8; 95% CI, 2.0-3.8) among women who used estrogen plus progestin after using unopposed estrogen therapy. Includes women who used both sequential estrogen plus progestin and continuous estrogen plus progestin (5 carcinomas and 3,718 person-years; RR, 1.6; 95% CI, 0.6-4.0) and unknown estrogen plus progestin regimen (15 carcinomas and 7,643 person-years; RR, 2.8; 95% CI, 1.6-4.8).

†Reference group for all exposures. All RRs adjusted for attained age, calendar time, household income, age at menarche, parity, duration of oral contraceptive use, current smoking, and BMI.

‡Unknown recency: 19 carcinomas and 7,250 person-years; RR, 3.5; 95% CI, 2.2-5.8. For sequential estrogen plus progestin and continuous estrogen plus progestin, comparison is no use versus current use and former use.

Table 3. RRs and 95% CIs associated with unopposed estrogen use

Unopposed estrogens	Carcinomas	Person-years	RR (95% CI)*
Ever-use[†]			
No use	168	209,196	1.0 (Reference)
Unopposed estrogens only	167	73,847	2.7 (2.2-3.4)
Estrogen, unknown progestins	66	29,576	2.5 (1.8-3.3)
Duration of use (y)[‡]			
No use	168	209,196	1.0 (Reference)
<5	71	52,715	1.7 (1.3-2.3)
5-9	38	11,839	4.5 (3.1-6.6)
≥10	57	7,587	10.7 (7.7-14.9)
P			<0.001
Excess RR per year			0.58 (0.42-0.79)
Time since last use[§]			
No use	168	209,196	1.0 (Reference)
Current user	63	9,451	10.8 (7.9-14.7)
Last use <5 y ago	22	13,608	2.5 (1.6-3.9)
Last use 5-9 y ago	24	14,452	2.2 (1.4-3.4)
Last use ≥10 y ago	43	29,468	1.5 (1.0-2.1)

*Adjusted for attained age, calendar time, household income, age at menarche, parity, duration of oral contraceptive use, current smoking, and BMI.

[†]Unknown hormone therapy use accounted for 12 cancers and 21,256 person-years (adjusted RR, 0.75; 95% CI, 0.42-1.35).

[‡]Restricted to women who never used hormones and women who used unopposed estrogens only. Unknown duration of use accounted for 1 cancer and 1,707 person-years (adjusted RR, 0.78; 95% CI, 0.11-5.62).

[§]Restricted to women who never used hormones and women who used unopposed estrogens only. Current use includes use within the previous year. Unknown time since last use accounted for 15 cancers and 6,869 person-years (adjusted RR, 2.4; 95% CI, 1.4-4.2). Person-year weighed mean durations of unopposed estrogen use were as follows: current users, 5.8 years; last use <5 years ago, 4.1 years; last use 5-9 years ago, 3.5 years; and last use ≥10 years ago, 2.9 years.

62 exposed controls. Another (8) observed an elevated but nonsignificant association with a continuous combined regimen (OR, 1.51; 95% CI, 0.67-3.42) based on 15 exposed cases and 14 exposed controls. Earlier case-control studies published null or inverse associations. A U.S. study of 833 cases produced null associations with continuous regimens (i.e., daily progestin) based on 94 exposed cases and 81 exposed controls (5). Another U.S. group reported positive associations with regimens that included progestins for ≤21 days per month (26) but a nonsignificant inverse association with continuous regimens (at least 25 days of progestin per cycle) based on 9 exposed cases and 33 exposed controls (OR, 0.6; 95% CI, 0.3-1.3; ref. 27). In an expanded analysis, which included 38 exposed cases and 123 exposed controls, associations with endometrial cancer were inverse for continuous regimens that included 2.5 mg/d medroxyprogesterone acetate (OR, 0.5; 95% CI, 0.3-0.7) and null for continuous regimens that included 5 or 10 mg/d medroxyprogesterone acetate (OR, 0.9; 95% CI, 0.4-1.9; ref. 9).

A large Swedish study that reported a significant inverse association with continuous regimens (at least 19 days of progestin per cycle; OR, 0.7; 95% CI, 0.4-1.0) was based on testosterone-derived progestins; the OR for progesterone-derived continuous progestins was 1.07 (95% CI, 0.86-1.33) and based on 1 exposed case and 9 exposed controls (6). Testosterone-derived progestins (e.g., norethisterone acetate), such as those included in regimens commonly used in Europe, may be more potent than progesterone-derived progestins (e.g., medroxyprogesterone acetate; ref. 28), which dominate the U.S. market. The most informative prospective observational data on estrogen plus progestin come from the United Kingdom's Million Women Study, which followed 716,738 postmenopausal hysterectomy-free British women for an average of 3.4 years. Of 242 women who developed endometrial cancer after using sequential estrogen plus progestins (10-14 days of progestins per cycle), all except 6 women reported use of regimens with testosterone-derived progestins. The associations with ever-use (RR, 1.05; 95% CI, 0.91-1.22) and current use (RR, 1.06; 95% CI, 0.85-1.32) were null, and the RR for ≥5 years of use was only slightly, and not significantly, elevated (1.17; 95% CI, 0.97-1.41). However, the significant inverse association with ever-use of continuous regimens (daily progestins; RR, 0.71; 95% CI, 0.56-0.90) did not differ by progestin derivation (testosterone-derived regimens, $n = 46$ cancers; RR, 0.76; 95% CI, 0.57-1.03; progesterone-derived progestins, $n = 27$ cancers; RR, 0.63; 95% CI, 0.43-0.93; ref. 13). Emergence of equally informative data from U.S. populations could help to resolve whether progestin derivation influences the true risk estimates.

Study timing might explain the increased risks reported in some recent observational data. Elevated breast cancer risks among estrogen plus progestin users first emerged in the mid-1990s to late 1990s (17, 29). Associations with less common outcomes, such as endometrial cancer, could take longer to emerge in population-based data. Although some early epidemiologic studies reported lower breast (30) and ovarian (31) cancer risks in hormone therapy users, subsequent larger studies that were conducted after hormone use increased (4) showed significantly increased risks (18, 32-35). Additional studies could test whether recent results are replicable.

Our study has limitations. The elevated RRs were based on relatively small numbers of women who developed endometrial carcinoma after using only estrogen plus progestin. We believe we accurately classified unopposed estrogen versus estrogen plus progestin formulations, but we obtained less-than-ideal data on estrogen plus progestin regimens. Sequential (i.e., cyclic) regimens traditionally included 5 to 15 days

Table 4. Duration and recency of unopposed estrogen only use

Duration of use (y)	Time since last use									
	No use		Current use		Last use <5 y ago		Last use 5-9 y ago		Last use ≥10 y ago	
	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
No use	168	1.0 (Reference)								
<5			8	2.8 (1.4-5.8)	9	1.5 (0.7-2.9)	13	1.7 (0.96-3.0)	32	1.5 (0.99-2.2)
5-9			19	14.0 (8.5-23.0)	5	3.6 (1.4-8.7)	5	2.8 (1.1-6.8)	8	2.3 (1.1-4.7)
≥10			36	22.0 (14.9-32.5)	8	6.2 (3.0-12.9)	6	5.7 (2.5-13.0)	3	2.3 (0.7-7.4)
Ave (y)				6.4		4.6		3.8		3.0
P				<0.001		<0.001		<0.001		0.007
Excess RR per year			1.43	(1.00-2.02)	0.37	(0.16-0.68)	0.44	(0.20-0.79)	0.19	(0.04-0.41)

NOTE: Restricted to women who never used hormones and women who used unopposed estrogens only. RRs adjusted for attained age, calendar time, household income, age at menarche, parity, duration of oral contraceptive use, current smoking, and BMI. Unknown duration or time since last use: 15 carcinomas (RR, 2.6; 95% CI, 1.5-4.4).

(usually <10 days) of progestin each cycle (5). Progestin exposure for at least 12 or 13 days per cycle is considered necessary to negate increased risks due to estrogens (36). The inclusion of both ''insufficient'' (i.e., <10 days) and ''sufficient'' (i.e., 13-14 days) progestin limits the generalizability of our sequential exposure group. However, our continuous estrogen plus progestin exposure group included women who took progestins at least 15 days, and as much as every day, per cycle. Our lower limit was less than that used in other studies (5-8, 27), but it represents putatively adequate progestins (37). Only our last mailed questionnaire (1995-1998) queried use of the continuous combined estrogen plus progestin pill, which emerged and gained popularity in the mid-1990s (38). Too few BCDDP participants reported its use to separately analyze this exposure.

We did not validate hormone therapy use, but other studies report good reliability for self-reported exposures (39). We could not verify compliance, and noncompliance among women who took both estrogen pills and progestin pills could have generated spurious or positively biased associations for both regimens (40). Low statistical power precluded us from determining whether duration, dose (for which we lacked complete information, although most of the reported estrogen doses were 0.3 or 0.625 mg/d and progestin doses were 2.5 mg/d), or regimen produced the estrogen plus progestin associations. These issues arise in virtually all current observational (and some experimental) hormone therapy studies. Other potential biases or unmeasured confounding may also exist.

Randomized clinical trials found no endometrial cancer risks among estrogen plus progestin users, but short follow-up and small numbers of events limit those data (41). The Women's Health Initiative estrogen plus progestin study, a large, randomized, double-blind, placebo-controlled clinical trial, tested continuous combined estrogen plus progestin (daily 0.625 mg/d conjugated equine estrogen plus 2.5 mg/d medroxyprogesterone acetate; $n = 27$ cancers) versus placebo ($n = 31$ cancers) in 16,608 postmenopausal women during a 5.6-year follow-up and yielded a hazard ratio of 0.81 (95% CI, 0.41-1.22; ref. 42). The 3-year Postmenopausal Estrogen/Progestin Interventions Trial randomized 596 women to placebo ($n = 119$), daily 0.625 mg/d conjugated equine estrogen ($n = 119$), or one of three estrogen plus progestin regimens ($n = 358$; ref. 43). Zero atypical hyperplasia lesions or carcinomas developed in estrogen plus progestin users.

Observational studies and clinical trials usually produce comparable estimates of treatment effects (44), including hormone therapy's cancer risks (10). However, for estrogen plus progestin and endometrial carcinoma, clinical trials and observational studies address different questions in different populations. The Women's Health Initiative performed pre-enrollment biopsies for all participants and excluded women with a thickened endometrial wall or any endometrial hyperplasia (42). Few women with complex or adenomatous hyperplasia (and even fewer with simple hyperplasia) subsequently develop endometrial cancer (45). However, for safety reasons (46), study medications were discontinued (and participants were referred to the local clinician for treatment) when a Women's Health Initiative participant developed complex, adenomatous, or atypical endometrial hyperplasia (and when a participant assigned to placebo developed simple hyperplasia). Participants assigned to estrogen plus progestin who developed simple hyperplasia had their study medications supplemented by 20 mg/d medroxyprogesterone acetate and received repeat endometrial biopsy within 6 months (42). By likely altering the natural history of endometrial carcinoma in hormone therapy trials, this level of surveillance and intervention complicates direct comparisons between clinical trial and observational study data.

None of the available observational studies has definitively evaluated the continuous estrogen plus progestin regimen used in the Women's Health Initiative and Postmenopausal Estrogen/Progestin Interventions trials. Observational studies may also capture an incomplete picture of endometrial cancer and estrogen plus progestin. Both sequential and continuous regimens cause increased irregular bleeding (47) and prompt gynecologic examinations to rule out cancer (42). A recent analysis postulated that hormone therapy's perceived coronary heart disease benefits could systematically influence observational study data collection and transform true hazards into observed benefits (48). An extension of this controversial (49) hypothesis could produce positively biased or false-positive associations between estrogen plus progestin and endometrial carcinoma in observational studies. If belief that continuous estrogen plus progestin does not increase risk (10, 36) affects early symptom reporting or delays diagnosis, then more early endometrial carcinomas—lesions that clinical trials might diagnose earlier (i.e., as hyperplasia, not cancer)—would be detected among estrogen plus progestin users in cohort studies. We could not directly test this hypothesis or explore whether it might account for the strength of the estrogen plus progestin associations in our data.

Endogenous progesterone and therapeutic progestins (50) inhibit most, but not all, estrogen-associated endometrial proliferation (51). Menopausal estrogen plus progestin induces atrophy in estrogen-stimulated endometrium, but other proliferative changes can persist (51, 52). Experimental and clinical studies differ regarding the apoptotic and antiproliferative effects of progestins in endometrial neoplasias (53, 54). Estrogen plus progestin might therefore promote existing lesions (55) or induce new lesions if continued estrogen exposure is genotoxic (56) or if supraphysiologic estrogen levels increase risk (57) regardless of absolute progestin levels (58). These and other possibilities warrant continued research.

The increased cancer risk among unopposed estrogen users seems firmly established (1) and declines after cessation of use. Consistent with studies that found similarly increased risk >5 (6), 8 (15), or 10 (7, 16) years after last unopposed estrogen use, women in our analysis remained at increased risk at least 10 years after cessation of use. Our study's large number of former users allowed us to assess recency and duration. The excess RR per year of use decreased across categories of time since last use, but longer durations of use increased risk regardless of time since last use. With a few exceptions, all combinations showed sustained elevated risks.

Our linear excess RR model showed significantly higher excess RRs per year of use in normal weight women than overweight or obese women. Some studies noted that pattern (7, 59). Others found no differences (16) or higher risks in heavier women (60, 61). The excess RRs per year of use did not differ by smoking, parity, and oral contraceptive use. Most studies showed similar null interactions (7, 16, 25, 60, 61). Some reported nonsignificant associations with smoking (25, 62-64).

In this study, estrogen plus progestin therapy, including regimens with at least 15 days of progestin per cycle, significantly increased endometrial carcinoma risk. Small sample sizes, inconsistent exposure definitions and divergent observational study results, and limited clinical trial data currently preclude definite conclusions about continuous estrogen plus progestin therapy's association with endometrial carcinoma. Despite substantial recent declines in menopausal hormone therapy use (38) and a favorable prognosis for most endometrial carcinomas, the potential risks suggest that women taking combination therapy require monitoring and evaluation for vaginal bleeding and signs of endometrial carcinoma. Women who use or used unopposed estrogen therapy, even for short durations, remain at increased risk and deserve continued surveillance during and after use.

Acknowledgments

We thank the BCDDP participants; Susan Englehart, M.S., and Catherine Ann Grundmayer, B.A., and the members of the BCDDP staff at Westat, Inc. (Rockville, MD); and Leslie Carroll, B.A., Franklin Demuth, B.S., and Jennifer Boyd-Morin, B.S., at IMS, Inc. (Silver Spring, MD) for computer support.

We acknowledge the California Department of Health Services, Cancer Surveillance Section; Florida Cancer Data System, under contract to the Florida Department of Health; Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; Michigan Cancer Surveillance Program within the Division of Vital Records and Health Statistics, Michigan Department of Community Health; Pennsylvania Department of Health; Tennessee Cancer Registry; Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina, Ohio, Oregon, and Rhode Island for providing data from their cancer registries for use in these analyses.

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